Research Article

Application of the Parametric Regression Model with the Four-Parameter Log-Logistic Distribution for Determining of the Effecting Factors on the Survival Rate of Colorectal Cancer Patients in the Presence of Competing Risks

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Abstract

Background: In competing risks data, when a person experiences more than one event in the study, usually the probability of experiencing the event of interest is altered. Therefore, it is necessary to analyze the competing risk data.

Objectives: The current study aimed at analyzing the colorectal cancer (CRC) risk factors based on competing risks model. The log-logistic model was also fitted with 2-parameter to evaluate the prognostic factors that affect the survival of patients with CRC, and comparisons were made to find the best model.

Methods: The current retrospective study was conducted on 1054 patients with CRC registered in the Research Institute of gastroenterology and liver disease center (from 2004 to 2015), Taleghani hospital, Tehran, Iran. The demographic and clinical features including age at diagnosis, gender, family history of CRC, body mass index (BMI), tumor size, and tumor site were extracted from the hospital documents. Analysis was performed using competing risks model and was based on the 4-parameter log-logistic distribution and log-logistic distribution. The analysis was carried out using R software version 3.0.3. P value less than 0.05 was considered as significant.

Results: Overall, 1054 patients with CRC and complete data were included in the analysis. The mean ± standard deviation (SD) of survival time was 92 ± 6.62 months. Out of the 1054 patients, 379 (36%) subjects died of CRC and 49 (4.6%) subjects died of other causes such as myocardial infarction, stomach cancer, liver cancer, etc. Four-parameter log-logistic model and log-logistic model with competing risk analysis indicated age at diagnosis and BMI as the prognosis.

Conclusions: The current study indicated age and BMI as prognosis of CRC, using a 4-parameter log-logistic model with competing risk analysis. Although the odds ratio (OR) in 4-parameter log-logistic model and log-logistic model ones were approximately similar, according to Akaike information criterion, the 4-parameter log-logistic model was more appropriate for survival analysis.

Keywords: Colorectal Cancer, Survival Analysis, Competing Risks, Parametric Models, Logistic Regression

1. Background

Cancer is 1 of the main reasons of death worldwide. Colorectal cancer (CRC) is 1 of the most wide-spreading and one of the major causes of cancer mortality worldwide (1). CRC is a public health burden, which involves 1 million new cases and causes half a million death each year (2). In the year 2015, it was the 2nd reason for cancer-related death in the United States with 132,700 new cases and 49,700 deaths (3).

The morbidity of CRC changed in Asian countries during the past few decades (4). CRC is rapidly rising in some of these developing countries as it has a higher rate compared with the developed countries (5). Unfortunately, the annual incidence of CRC in the Asian countries is expected to increase over the next two decades (6, 7). In addition, the survival rate is higher in the developed countries rather than the developing countries (8).

In Iran, CRC is the 3rd most prevailing one, which its incidence increased during the past 3 decades and according to the recent studies it has a rapid rise, particularly among

young patients with higher rate than expected (9, 10). This caused the CRC to be a major health problem in Iran (11). According to the Iranian annual national cancer registration report, the colorectal cancer is the 3rd prevailing cancer in females and the 5th in males in Iran (12).

Survival analysis is the analysis of data measured in a specific time of origin until an event of interest or a specified endpoint (13). In many prognostic studies, patients are exposed to different events. In a study entitled "The effects of tumor stage at diagnosis and treatment on survival in breast cancer", other causes were the reasons of death in many subjects rather than breast cancer itself. What obstructs the observation of the main event "death of breast cancer" is the event "death of other causes". Cancer stage and treatment should be noted as they have different effects on mortality because of other causes. The accurate and authentic analysis of these researches should be considered for competing the risks of death of other causes (14). In competing risks data, when a person experiences more than one event in the study, usually the probability of experiencing the event of interest is altered (15).

Different non-parametric, semi-parametric, and parametric models can be used to estimate survival rate in the presence of competing risks (16). Many researchers try to choose semi-parametric (or non-parametric) models rather than parametric ones; and the patients died of CRC are considered as censored ones instead of competing risks (17). This situation, however, is not a type of censoring. In the process of censoring the main event still happens at a later time, but maybe could not be observed at the time of happening. Therefore, the analysis of competing risk data is necessary (18).

Based on the flexible competing risks model, Belot et al. evaluated 4115 patients diagnosed with CRC to identify the CRC-associated risk factors. In their study, 1618 died of CRC, and 1217 of other causes. Only the age at diagnosis had a significant effect on survival time (14). Akhoond et al., also compared survival and prognostic factors in patients with CRC, and it was the cause of death in all subjects. The results of their study showed that some variables may have a different impact on CRC (19). Another study conducted by Shigeta al., compared the effects of laparoscopic surgery and open surgery on the patterns of death in the elderly patients with CRC, and the risk factors for the types of death were estimated using a competing risks analysis (20). Fine and Gary competing risk regression model was applied by Baghestani et al., to determine the factors affecting the survival of patients with CRC. The results of their study indicated that just age at diagnosis was the significant prognosis factor for CRC (18).

The parametric model is studied assuming that the competing risks follow different lifetime distributions such as exponential, gamma, and Weibull (21). Although the Cox regression model and the Kaplan-Meier method are the popular techniques for survival analysis, ignoring competing risks causes bias in the model results. The susceptibility of such analyses to biased estimates, when competing events are present, may be less known (22). Therefore, alternative methods specifically designed for analyzing competing risks data that consider competing events (such as parametric models) should be applied (23).

One of the advantages of using the parametric methods rather than non- and semi-parametric methods is as follows: When the parametric model is selected correctly, it is possible to predict the event occurrence probability in long term and have a clear picture of survival time (or the time to failure) and hazard function. Also, as the survival pattern follows a special parametric model, the acquired estimates are more accurate than non- or semi-parametric estimates (24). The 4-parameter log-logistic distribution is a distribution with an extra parameter (compared to classic log-logistic), which could be more flexible to analyze competing risks model due to its ability to cover different types of hazard functions (25).

2. Objectives

The current study aimed at assessing the association between survival of patients with CRC and prognostic factors in a competing risks parametric model using the 4-parameter log-logistic distribution. The log-logistic model was also fitted with 2-parameter to evaluate the prognostic factors that affected the survival of patients with CRC, and comparisons were made to find the best model.

3. Methods

3.1. Study Population

Data for the current retrospective study were provided by Taleghani hospital, Tehran, Iran. A total of 1456 patients with CRC referred to Taleghani Hospital from January 2004 to January 2014; the patients were followed-up until April 2015, and their survival status was identified.

Checking the latest situation (death and the causes of death) of registered patients in the data bank of gastroenterology institute is a regular plan and each year this telephone checking is done once or twice. During this process, the person in charge tries to get sufficient information regarding the issue of death, main cause of death, and the date. Some patients, due to wrong phone number, relocation of the residence, and incompliance of their families were excluded from the analysis. In addition, the patients with incomplete filing at hospital registry, and lack of risk

factors included in the study had not been recorded; therefore, their data were excluded from the analysis. The data of 1054 patients with complete filing were selected for the study. Patients with complete records such as age at diagnosis, gender, family history of CRC, body mass index (BMI), tumor size, and tumor site were enrolled into the study. Finally 402 patients were excluded from the study and no sample size was calculated for the current survival analysis. Most patients were from Tehran province. The ethical committee of gastroenterology and liver diseases research center of Shahid Beheshti Medical University approved the current study (ID no. 1157).

The current article focused on the CRC-related deaths, and therefore other causes of death were intended to be competing risks. The demographic and clinical features were extracted from the hospital files; including age at diagnosis, gender, family history of CRC, BMI, tumor size, and tumor site. BMI values (kg/m²) were grouped into the 4 categories of the world health organization (WHO) (26): underweight (BMI < 18.5), normal (18.5 - 24.9), overweight (25.0 - 29.9), and obese ($\geq$ 30.0).

3.2. Statistical Analysis

In parametric survival model, survival time (outcome) assumed to follow some distribution such as weibull, log-logistic,ect. (13). Four-parameter log-logistic distribution including α and θ, in addition to 2 parameters of λ and τ, possesses enough flexibility and can cover different forms of hazard function. This is an important characteristic of the 4-parameter log-logistic distribution that differs from the 2-parameter log-logistic distribution.

In analyzing the competing risks data for each person there is one type of failure (type of event), in addition to failure time (survival time). The failure time (T) is assumed to be a continuous and positive random variable, while the failure cause (k) takes values in the finite set (k $\geq$ 2) j=1,…,k. For CRC data, the 1st cause of failure (die of CRC, j = 1) was considered as the main event in the survival model, and the 2nd cause (die of other events, j = 2) was considered as the competing risks. It was assumed that survival time of each competing risks had 4-parameter log-logistic distributions. The survival function for each of the competing risks (the cause of failure of j) was defined as follows (25):

$$j = 1, 2…, \theta > 0, \lambda > 0, \tau > 0, -\infty < \alpha < \infty$$

To assess the effects of gender, age at diagnosis, family history of CRC, BMI, tumor size, and tumor site on the survival time, the scale parameter λj was defined as a linear combination of covariates. The estimate of parameters was done through the maximum likelihood approach. Log-logistic distribution can be considered as a special case of 4-parameter log-logistic distribution, because when α =1 and θ = 1, this distribution is changed to a log-logistic

distribution with 2 parameters (λ, τ). In competing-risks setting, the inadequacy of the Kaplan-Meier curve is due to the Kaplan-Meier estimation as it assumes the outcome risk of censored cases as that of the other cases in the study (27). In this case, the cumulative incidence function's curve (CIFs curve) is a better choice instead of survival function; thus, the current study used it (28). Cumulative incidence is defined as the probability of occurrence of a particular event, such as the occurrence of a particular disease, before a given time (29). To select the best model, Akaike information criterion (AIC) and the likelihood ratio test (LRT) statistics were used. Lower AIC indicates better likelihood and a better model (30). P value < 0.05 was considered as statistically significant and the computer program was written in the software R version 3.0.3.

4. Results

Among the 1059 subjects of the study, 613 (58.2%) were male and 441 (41.8%) female, and 44.8% had a family history of cancer. The primary site of tumor for 524 (49.7%) patients was colon, while in 530 (50.3%) patients it was rectum. Log rank test showed a better survival for females, people with a BMI between 25 and 29.9 kg/m², patients with colon tumor site, the ones who were under 53 years old, patients within a family history of cancer, and patients with tumor size less than 1 cm (Table 1).

In recent follow-ups, it was found that 379 (36%) patients died of CRC, 49 (4.6%) died of other causes such as myocardial infarction, stomach cancer, liver cancer or kidney and lung diseases, and 626 (59.4%) subjects survived until the end of the study. Survival time was calculated in months and was represented as mean $\pm$ standard deviation (SD). The mean $\pm$ SD of survival for patients who died of CRC was 92 $\pm$ 6.62 months (95% confidence interval (CI); 79.02 - 104.98). Also, the mean $\pm$ SD age at diagnosis was 53.69 $\pm$ 15.09 years (ranged 16 to 97 years).

In the next stage, data were fitted into a multivariate model using 4-parameter log-logistic and log-logistic regression. Variables such as BMI and age at diagnosis that had a significant influence on survival of CRC are presented in Table 2. In regards to odds ratio (OR), it was found that people with a BMI between 25 and 29.9, and people with a BMI higher than 30 kg/m² were less susceptible to die of CRC than the patients with a BMI less than 18.5 kg/m² (P value < 0.05).

Figure 1 presents the survival plot of patients with CRC according to the 4-parameter log-logistic competing risks model for different ranges of BMI, indicating higher survival of patients with a BMI between 25 and 29.9 kg/m² and people with a BMI higher than 30 kg/m² than people with a BMI less than 18.5 kg/m².

$$S_{j\left(t,\lambda_j,\tau_j,\theta_j,\alpha_j\right)} = exp\left\{-\frac{\theta_j^2}{\alpha_j}\left[\left(\frac{\log\left(1+\lambda_j t^{\tau_j}\right)}{\theta_j}+1\right)^{\alpha_j}-1\right]\right\} \tag{1}$$

Table 1. Demographic and Clinical Factors of Patients with Colorectal Cancer and the Results of Log Rank Test for Univariate Analysis

| Prognostic Factors	Number of Patients, No. (%)	Death of CRC	Death of Other Risks	Survival Time, Mean (SD)	P Value
BMI, kg/m^2					< 0.001
< 18.5	54 (5.1)	17 (31.5)	6 (11.1)	120.72 (17.37)	
18.5 - 24.9	535 (50.8)	193 (36.1)	55 (10.3)	119.23 (9.50)	
25 - 29.9	361 (34.3)	92 (25.5)	34 (9.4)	207.32 (11.27)	
> 30	104 (9.9)	23 (22.1)	5 (4.8)	176.59 (14.46)	
Tumor site					0.10
Colon	524 (49.7)	170 (32.4)	36 (6.9)	168.04 (11.80)	
Rectum	530 (50.3)	155 (29.2)	64 (12.1)	133.05 (19.61)	
Family history					0.14
Yes	472 (44.8)	152 (32.2)	28 (5.9)	182.86 (12.40)	
No	582 (55.2)	173 (29.7)	72 (12.4)	126.0 (12.97)	
Age at Diagnosis					< 0.001
> 60	384 (36.4)	143 (37.2)	33 (8.6)	90.45 (4.88)	
< 60	670 (63.6)	182 (27.2)	67 (10)	176.01 (11.13)	
Gender					0.013
Male	613 (58.2)	197 (32.1)	69 (11.3)	142.43 (10.66)	
Female	441 (41.8)	128 (29)	31 (7)	168.74 (13.12)	
Tumor size, cm					0.025
< 1	168 (15.9)	56 (33.3)	3 (1.8)	203.702 (17.63)	
> 1	886 (84.1)	269 (30.4)	97 (10.9)	144.09 (9.61)	
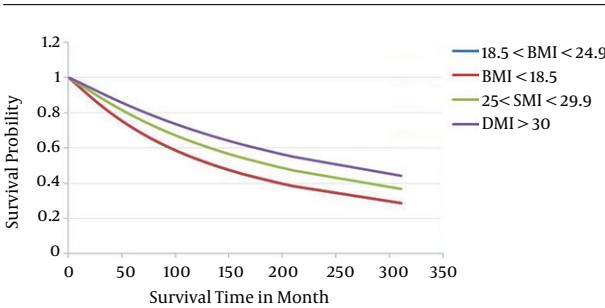
Figure 1. Estimated Survival Curves for Different Ranges of BMI in Patients with CRC, Based on a Competing Risk Model

Figure 2 presents the cumulative incidence function (CIF) curve of patients with CRC according to the 4-parameter log-logistic competing risks model, which considered the cutoff point of 60 years for patients, indicating less susceptible to death of CRC for patients who were less than 60 years old. Other factors such as tumor site, tumor size, gender, and family history of CRC had no significant association with the survival time of patients with CRC in both 4-parameter log-logistic model and log-logistic model (Table 2). To make a comparison between the 2 parametric models, AIC and LRT were used in the current study. Based on AIC, 4-parameter log-logistic model is more favorable for the survival analysis of patients with CRC. Moreover, based on the LRT, the efficiency of competing risk 4-parameter log-logistic model for the data set of colorectal cancer was evaluated. Therefore, the value $X_L = 2L_{FL} - 2L_L = 5.95$ had a Chi-square distribution with 2 degrees of freedom and the P value < 0.001. It was concluded that based on the values of X_L and the P value, the 4-parameter log-logistic distribution fitted the data better than log-logistic distribution.

Table 2. Prognostic Factors Related to Survival of Patients with Colorectal Cancer

Prognostic Factors	Four-Parameter Log-Logistic Model			Log-Logistic Model		
	Coefficient (SE)	OR (95% CI)	value	Coefficient (SE)	OR (95% CI)	P value
BMI, kg/m²						
< 18.5		1			1	
18.5 - 24.9	0.02 (0.078)	1.02 (0.87 - 1.18)	0.16	-0.008 (0.09)	0.99 (0.83 - 1.18)	0.92
25 - 29.9	-0.27 (0.11)	0.76 (0.62 - 0.93)	0.009	-0.37 (0.13)	0.68 (0.53 - 0.88)	0.002
> 30	-0.48 (0.19)	0.62 (0.42 - 0.91)	0.01	-0.68 (0.24)	0.51 (0.31 - 0.82)	0.005
Tumor site						0.82
Colon		1			1	
Rectum	-0.006 (0.081)	0.99 (0.84 - 1.16)	0.94	-0.23 (0.95)	0.97 (0.81 - 1.17)	
Family history						0.86
Yes		1			1	
No	0.16 (0.086)	1.18 (0.99 - 1.39)	0.93	0.15 (0.10)	1.16 (0.95 - 1.42)	
Age at Diagnosis						0.001
< 60		1			1	
> 60	-0.49 (0.074)	0.61 (0.52 - 0.71)	< 0.001	-0.56 (0.08)	0.57 (0.47 - 0.67)	
Gender						0.26
Female		1			1	
Male	-0.117 (0.09)	0.81 (0.74 - 1.06)	0.19	-0.12 (0.107)	0.88 (0.71 - 109)	
Tumor size, cm						
< 1		1			1	0.87
> 1	-0.02 (0.14)	0.98 (0.74 - 1.29)	0.87	-0.027 (0.16)	0.97 (0.71 - 1.34)	
τ	0.93 (0.02)	2.52 (2.46 - 2.60)	< 0.001	1.11 (0.02)	3.05 (2.96 - 3.15)	<0.001
θ	0.005 (0.001)	1.004 (1.00 - 1.01)	< 0.001	-	-	-
α	1.79 (0.01)	6.02 (5.90 - 6.15)	< 0.001	-	-	-
AIC	5423.706			5427.118		

5. Discussion

The problem of competing risks is a serious case in survival analysis. In situations that the subjects are exposed to more than 1 cause of failure, the competing risks models should be used instead of other models and common approaches of survival analysis. The subjects who fail in other competing risks are treated as censored subjects in the Cox regression model (31). Moreover, parametric model flexibility is beneficial for competing risks survival analysis, especially in the cases that the proportional hazards assumption in the Cox proportional hazards (PH) model is inappropriate and the hazard function shape is unclear (14).

Wahed et al., used the generalized Weibull model for competing risks data of breast cancer (32), and Mazucheli et al., based on the Lindley competing risks model, evaluated the covariate effects on survival time in patients with

squamous cell carcinoma (33). Also, in another study, Baghestani et al., applied Weibull model in the presence of competing risks for CRC data (34). The current study aimed at investigating the prognostic factors of survival of patients with CRC in the presence of competing risks, using the 4-parameter log-logistic distribution. In these data there were 5 different failures; die of CRC, myocardial infarction, and cancer, or kidney and lung diseases.

Although both 4-parameter log-logistic and log-logistic models in the current study indicated the same significant results for age at diagnosis and BMI, according to AIC, 4-parameter log-logistic model and LRT showed better fit into the data. Also, the 95% confidence intervals for the prognostic factors based on the 4-parameter log-logistic model were shorter compared to those of the log-logistic model considering the competing risks. There-
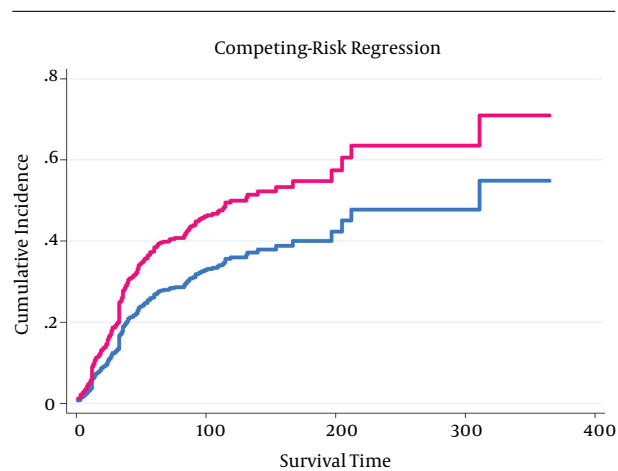
Figure 2. Competing-Risks Regression; Cumulative Incidence Functions of 1054 Patients with CRC, Separated by Age at Diagnosis

fore, the 4-parameter log-logistic model in the presence of competing-risks was more accurate.

In the current study, BMI and age at diagnosis of the disease were prognostic factors of CRC survival, according to the parametric regression model, and AIC and LRT indicated that the 4-parameter log-logistic competing risks model was the best option among parametric models to analyze the survival of patients with CRC admitted to Taleghani hospital. The results of the current study can be generalized to the population of Iran.

In the current study data, the mean age at the time of diagnosis was about 53.69 ± 15.09 years, which was exactly similar to that of Asghari Jafarabadi's study (11), while this mean was not in line with other Iranian published reports (17). In both univariate and multivariate analyses, age at diagnosis was a strong and independent prognostic factor for CRC and showed an increased risk of death for the patients who were above 60 years at diagnosis and indicated better survival rates in young patients. This finding was similar to the result of many studies (35, 36) that indicated better survival rates in young patients. Also, Mehrkhani showed that the patients under 65 years had a longer survival period than the ones over 65, and CRC in older patients was usually diagnosed at a late stage (37).

In the univariate analysis, patients with BMI of 18.5 to 24.9 kg/m² had worse outcome and the patients with BMI of 25 to 29.9 and > 30 kg/m² had better outcome than the patients with reference group of <18.5 kg/m². But, results of multivariate analysis (in both parametric models) indicated that with regards to OR, the people with a BMI between 25 and 29.9 kg/m² or higher than 30 kg/m² were less susceptible to death of CRC than people with a BMI lower than 18.5 kg/m². It was contrary to the results of the study

Nilson. They did not find any relationships between BMI and risk of CRC (38). While Hines et al., reported higher mortality from CRC in underweight patients (39).

Kroenke et al, evaluated the association between BMI and CRC outcomes. They assessed 3408 patients with CRC, aged 18 to 80 years with stage I to III CRC. They indicated that BMI at diagnosis of CRC was associated with all causes and disease-related mortality (40).

Also Walter et al., in a large population-based cohort study on patients with CRC evaluated the associations between BMI at diagnosis and pre-diagnostic BMI changes with relevant prognostic outcomes. Their research revealed that overweight and obesity were associated with increased survival after a CRC diagnosis. A major decrease in BMI in the years before diagnosis of CRC was a strong independent predictor of decreased survival time of patients (41).

Gender was not a significant predictor of patients' survival according to all models. In most countries, incidence and mortality rates were considerably higher in males than females (42); log rank test showed a better survival of females. Also, several studies reported superior survival in females (43, 44); while, other studies did not report any differences (45).

Tumor size was a significant factor for CRC in univariate analysis, but it was not significant in multivariate analysis. In a study by Zhou et al. (46), a significant difference in tumor size was reported between sub-sites of CRC. Another study (47) also reported the same conclusion of tumor size in a univariate analysis.

Tumor site of CRC was another risk factor in the current analysis. Some studies reported a better survival rate of colon cancer (48). However, in the current study, tumor site was not a significant factor in any parametric models. It was in contrast to some Iranian studies (41).

Although in the current study a family history of the cancer was not a significant prognostic factor of CRC, some controversies exist (49).

The prognostic factors included in the current study had all complete data in hand. One of the limitations of the study was the lack of access to some information, such as the number of metastasis sites, the stage at diagnosis, grade of tumor, etc., which could have important effects on the survival rate of patients with CRC. Changing address and phone numbers for follow-up were other limitations of the study. For future studies, this information would be included in competing risks survival for better prediction.

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Footnote

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